Rapid and Stereocontrolled Synthesis of Racemic and Optically Pure Highly Functionalized Pyrrolizidine Systems via Rearrangement of 1,3-Dipolar Cycloadducts Derived from 2-Azetidinone-Tethered Azomethine Ylides

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This work describes a convenient procedure for the straightforward preparation of polyfunctionalized enantiopure pyrrolizidine systems. The methodology capitalizes on a HCl(g)-promoted reaction of the 1,3-dipolar cycloadducts derived from 2-azetidinone-tethered azomethine ylides, smoothly affording different types of highly functionalized bi- and tricyclic systems in racemic and optically pure forms. This process involves a selective bond cleavage of the four-membered ring, followed by a rearrangement under the reaction conditions. The synthetic route employed was shown to be compatible with a variety of 4-oxoazetidine-2-carbaldehydes, α-amino esters, or dipolarophiles, offering a versatile entry to pyrrolizidine systems.

Introduction

1,3-Dipolar cycloaddition employing azomethine ylides is an important process in organic synthesis, acquiring a prominent place of synthetic strategy for a variety of targets, including natural products such as azasugars and alkaloids.[1] Natural products having the 1-azabicyclo-[3.3.0]octane skeleton (pyrrolizidine alkaloids) are widespread in nature, occurring in various plant species and in insects. Their structural and stereochemical complexity, coupled with their diverse and potent biological activities,[2] make pyrrolizidine alkaloids as well as structurally related unnatural compounds very attractive synthetic targets.[3] In addition, angular fused tricycles represent a structurally intriguing unit present in many natural products, and among prominent targets of this class of compounds are triquinanes.[4] Moreover, functionalized bicyclic lactams structurally related to pyrrolizidine and indolizidine have been developed as conformationally restricted peptide mimetics,[5] and a chiral pyrrolizidine base has been used as a catalyst in the asymmetric Baylis−Hillman reaction.[6] On the other hand, the importance of 2-azetidinones as synthetic intermediates has been widely recognized in organic synthesis. This usefulness is based on the impressive variety of transformations that can be accomplished with this system.[7] The application of β-lactams in stereoselective synthesis may be divided into two groups, namely,

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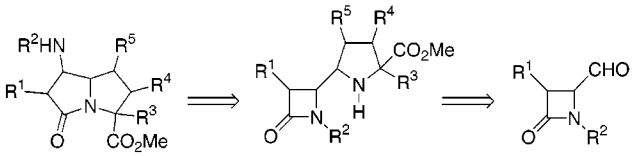
Scheme 1



those processes based on transformation of the 2-azetidinone by external reagents and those based on rearrangements of the four-membered ring. The first type of reactivity is exemplified by the β-lactam synthon method.[8] The second group of reactions is based on the building of a conveniently functionalized 2-azetidinone to produce different types of usually cyclic compounds by selective bond breakage and rearrangement.[9] Despite the versatility of the 2-azetidinone ring, there is little information available on the use of β-lactams as chiral synthons for the synthesis of pyrrolizidine alkaloids, with only Reuschling[10] and Palomo[11] having reported β-lactam routes to simple pyrrolizidines. At the outset of the present studies,[12] no information was available regarding the 1,3-dipolar cycloaddition reaction involving 4-oxoazetidine-2-carbaldehydes-derived azomethine ylides.[13] Our interest in the use of 4-oxoazetidine-2-carbaldehydes as substrates for addition reactions and cyclization processes[14] prompted us to evaluate the combination of the [3 + 2] cycloaddition reaction of *N*-metalated azomethine ylides with rearrangement reactions in the 2-azetidinone ring as a route to complex pyrrolizidine derivatives. We wish to report now full details of the straightforward asymmetric synthesis of different highly functionalized pyrrolizidine and diazatriquinane systems using β-lactams as chiral building blocks. A brief retrosynthetic analysis for the pyrrolizidine unit is illustrated in Scheme 1.

Results and Discussion

Rearrangement precursors, 4-oxoazetidine-2-carbaldehydes **1**, were prepared both in the racemic form and in optically pure form using standard methodology. Racemic compounds **1a**−**c** were obtained as single *cis*-diastereoisomers, following our one-pot method from *N*,*N*-di-(*p*-methoxyphenyl)glyoxal diimine.[15] 3-Unsubstituted β-lactam **1d** was obtained following a previously reported procedure.[16] Enantiopure 2-azetidinone (+)-**1e** was conveniently synthesized as a single *cis*-enantiomer from *N*-(4-methoxyphenyl)-(*R*)-2,3-*O*-isopropylidenepropanimine, through Staudinger reaction with methoxyacetyl chloride in the presence of Et_3N,[17] followed by simple transformations of the acetal moiety.[14] Treatment of aldehydes **1** with various α-amino esters in the presence of 4 Å molecular sieves provided the corresponding aliphatic aldimines **2**. Imines **2** were obtained in quantitative yields and were used for next step without further purification. The goal of this work has been to use structurally diverse pyrrolidinyl-β-lactams, obtained from 2-azetidinone-tethered alanine (glycine)-derived azomethine ylides, as useful synthetic intermediates for the straightforward entry to the final target, pyrrolizidine systems. The 1,3-dipolar cycloaddition was achieved via metal ion catalysis at room temperature. Treatment of aldimines **2** with the appropriate dienophile (e.g., phenylmaleimide, methyl acrylate, dimethyl fumarate, and *trans*-β-nitrostyrene) in the presence of AgOAc/Et_3N in toluene at room temperature for 40 h gave with reasonable diastereoselectivity mixtures of cycloadducts **3** and **4** (see Tables 1−3) in moderate to good yields (45−80%).[18] Furthermore, the reaction with the unsymmetric monoactivated alkene, methyl acrylate, proceeded with total regioselectivity. The reaction with the less activated dipolarophile dimethyl acetylenedicarboxylate was not effective at room temperature and as a consequence the adducts (+)-**3k** and (+)-**4k** were not obtained. However, when the experiment was carried out at 40 °C a good result was achieved (Scheme 2). Fortunately, in all cases the diastereomeric cycloadducts **3** and **4** could be easily separated by gravity flow chromatography, the isomeric products **3** being the less polar compounds.

The steric properties of the C3 substituent on the 2-azetidinone ring appear to influence the stereoselectivity of the cycloaddition, sterically less demanding groups increasing the diastereoisomeric ratio (see Tables 1 and 2). In addition, no adducts were obtained placing a *tert*-butyl group at C3 in the 2-azetidinone azomethine ylide.

When DBU was used instead of Et_3N complex mixtures of unidentified products were obtained, whereas pyridine gave erratic results. Besides, perfoming the reaction in acetonitrile afforded poor yields of cycloadducts.

To successfully achieve our initial aim, we needed to find an expedient transformation of the cycloadducts into pyrrolizidine and diazatriquinane systems. First, sodium methoxide was tested as reagent for the conversion of adducts **3** or **4** into the framework of pyrrolizidine alkaloids. In the event, the pyrrolizidine skeleton was obtained from maleimide-derived cycloadduct **3a**, affording compound **5** but after chemoselective epimerization

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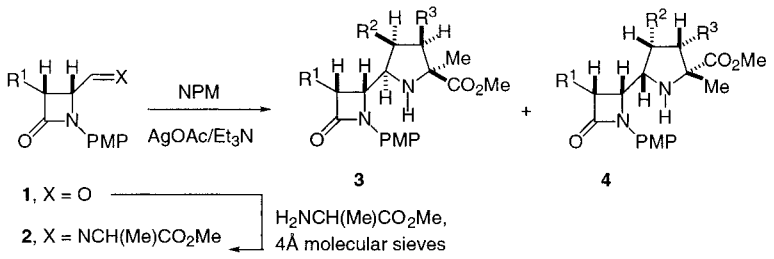
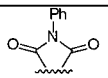
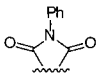
(18) The origin of the facial selectivity of the reaction between metalloazomethine ylides and dipolarophiles has been proposed as the result of an *endo*-specific cycloaddition of the *E*,*E*-dipole generated under kinetic control: see ref 13. The stereochemical outcome of the [3 + 2] cycloaddition between *N*-metalated azomethine ylides and nitroalkenes has been suggested as the result of a tandem Michael−Henry process: see ref 1k.

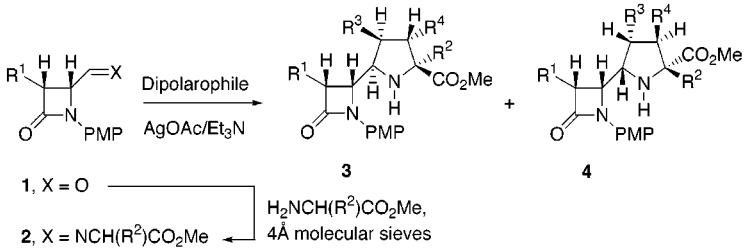
Table 1. Synthesis of Rearrangement Precursors, Pyrrolidinyl-β-lactams 3a,b and 4a,b[a]



Entry	Aldehyde	R^1	R^2	R^3	Products	**3/4** ratio[b]	Yield **3/4** (%)[c]
1	**1a**	Ph			**3a/4a**	55 : 45	25/20
2	**1b**	allyl			**3b/4b**	90 : 10	45/5

[a] NPM = *N*-Phenylmaleimide. PMP = 4-$MeOC_6H_4$. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [c] Yield of pure, isolated product with correct analytical and spectral data.

Table 2. Synthesis of Rearrangement Precursors, Pyrrolidinyl-β-lactams 3c−h and 4c−h

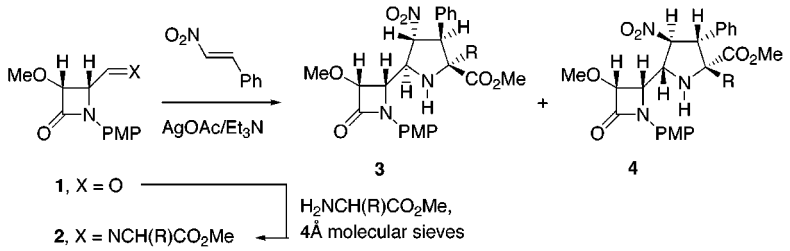


entry	aldehyde	R^1	R^2	R^3	R^4	products	**3/4** ratio[a]	yield **3/4** (%)[b]
1	**1c**	vinyl	H	CO_2Me	H	**3c/4c**	95:5	43/2
2	**1d**	H	Me	CO_2Me	H	**3d**[c]	c	48[d]
3	(+)-**1e**	MeO	Me	CO_2Me	H	(+)-**3e**/(+)-**4e**	65:35	39/21
4	(+)-**1e**	MeO	H	CO_2Me	H	(+)-**3f**/(+)-**4f**	70:30[e]	46/20
5	(+)-**1e**	MeO	Me	CO_2Me	CO_2Me	(+)-**3g**/(+)-**4g**	58:42	45/33
6	(+)-**1e**	MeO	H	CO_2Me	CO_2Me	(+)-**3h**/(+)-**4h**	79:21[f]	53/14

[a] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. PMP = 4-$MeOC_6H_4$. Pyridine was used instead of Et_3N for adducts **3c**/**4c**. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] The ^1H NMR spectrum of the crude mixture showed mainly **3d** together with unmeasurable traces of two other isomers. [d] Additional fractions containing the major cycloadduct together with traces of the minor isomers were isolated after column chromatography, accounting for an overall 80% yield. [e] Two additional diastereoisomeric cycloadducts were detected in the ^1H NMR spectrum of the crude reaction mixture, accounting, respectively, for 7% and 4% of the products formed. [f] An additional diastereoisomeric cycloadduct was detected in the ^1H NMR spectrum of the crude reaction mixture, accounting for an 8% of the products formed.

at C4 in the former β-lactam ring (Scheme 3). However, partial epimerization was observed for methyl acrylate and dimethyl fumarate derived cycloadducts. This preliminary result encouraged us to find a more convenient reagent for this transformation. Then, attempts were made to improve the method by using acidic conditions. To our delight, when the reaction was conducted in a saturated solution of HCl(g) in 2-propanol at room temperature during 36 h, it gave rise to racemic and optically pure pyrrolizidine systems **6** and **7** in moderate to good yields and without byproducts (Schemes 4 and 5). However, some isopropyl transesterification was observed by treatment of adducts (+)-**3h** and (+)-**4f** under the usual conditions of HCl(g) in 2-propanol. The reaction of pyrrolidinyl-β-lactam (+)-**3h** with HCl(g) in 2-propanol afforded the transesterificated tricycle (+)-**6f** as the only product. The obtention of bicycle (−)-**7b** was more efficiently achieved via reaction of adduct (+)-**4f** in a saturated methanolic solution of HCl(g). The reaction of compounds (+)-**3f** and (+)-**3k** in a saturated solution of HCl(g) in methanol for 36 h gave in quantitative yield compounds (+)-**8** and (−)-**9**, respectively, as crude product. Product (+)-**8** has a monocyclic pyrrolidine structure, which required 2 h of heating in toluene under PTSA catalysis using a Dean−Stark apparatus to give the expected pyrrolizidine system (+)-**6d**. By contrast, pyrroline (−)-**9** under PTSA catalysis gave a complex reaction mixture, bicycle (+)-**10** being a very minor component. Pyrrolidine (+)-**8** slowly evolves on standing to the tricycle (+)-**6d**. Tricycle (+)-**6d** and bicycle (+)-**10** were alternatively obtained in yields of 50% and 52%, respectively, via heating overnight the adducts (+)-**3f** and (+)-**3k** in methanol under 37% aqueous hydrochloric acid catalysis (Scheme 6). Compound (+)-**3i** derived from *trans*-β-nitrostyrene and alanine by treatment with HCl(g) failed to give the pyrrolizidine system, while reaction of pyrrolidinyl-β-lactam (+)-**3j** derived from *trans*-β-nitrostyrene and glycine, in a saturated 2-propanolic solution of HCl(g), smoothly provided in 59% yield the pyrrolizidine lactam (+)-**11a**. Cycloadduct (+)-**4i** was

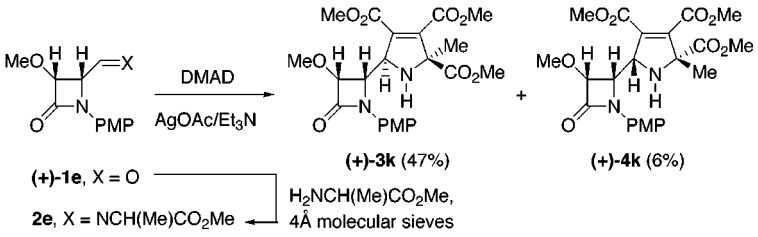
Table 3. Synthesis of Rearrangement Precursors, Pyrrolidinyl-β-lactams 3i,j and 4i,j



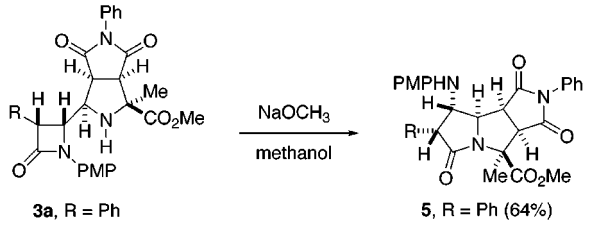
entry	aldehyde	R	products	**3/4** ratio[a]	yield **3**/**4** (%)[b]
1	(+)-**1e**	Me	(+)-**3i**/(+)-**4i**	52:48[c]	25/23
2	(+)-**1e**	H	(+)-**3j**/(+)-**4j**	82:18[d]	41/9

[a] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures before purification. PMP = 4-MeOC$_6$H$_4$. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] An additional diastereoisomeric cycloadduct was detected in the ^{1}H NMR spectrum of the crude reaction mixture accounting for 10% of the products formed. [d] An additional diastereoisomeric cycloadduct was detected in the ^{1}H NMR spectrum of the crude reaction mixture accounting for 8% of the products formed.

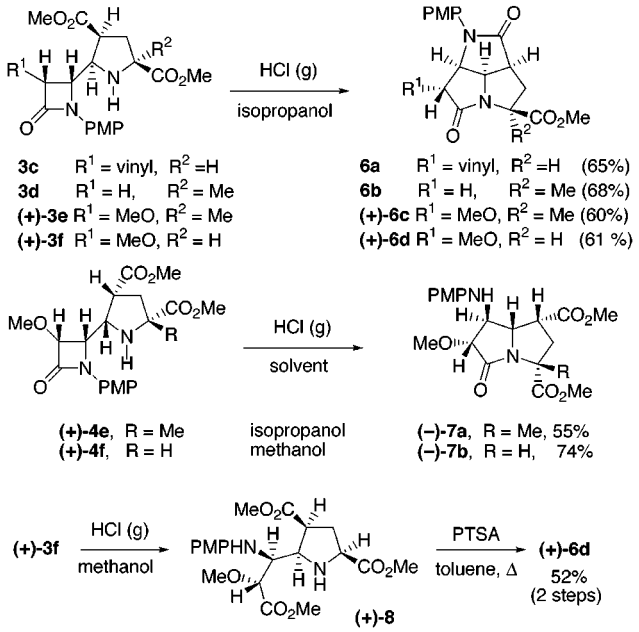
Scheme 2



Scheme 3



Scheme 4

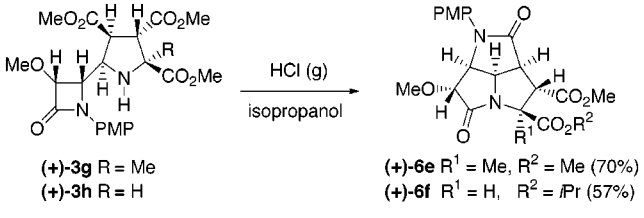


dissolved in 2-propanol and was converted in good yield (70%) to pyrrolizidinone (+)-**11b** by treatment with HCl-(g). Regiospecific epimerization at hydrogen α to the bridge nitrogen atom (H^c) was observed on compound (+)-**11a**, while chemospecific epimerization at hydrogen α to the nitro moiety (H^d) was observed on compound (+)-**11b** (Scheme 7 and Figure 3). The formation of pyrrolizidine lactams **5**−**7** and **10** and **11** involves a selective C−N bond cleavage at the four-membered ring, followed by a rearrangement under the reaction conditions. The overall transformation must be driven by relief of the strain associated with the four-membered ring, on forming more stable polycyclic systems. The relative *anti*-disposition of the ester and amine moieties in bicycles **7** and **10** must be responsible for the failure of the third cyclization to occur, preventing the formation of a highly strained tricyclic system.

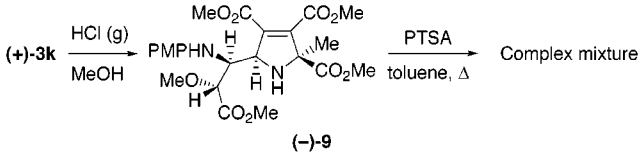
Configurational Assignment for Bi- and Tricyclic Systems. The polycyclic structures (by DEPT, HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings and NOE experiments) of diazatriquinanes **6** and pyrrolizidines **5**, **7**, and **10** were established by NMR one- and two-dimensional techniques. Taking into account that separated diastereomeric cycloadducts **3** and **4** could be obtained and cyclized, the stereochemistry for compounds **3** and **4** was inmediately deduced by comparison with the NOE results of the polycyclic systems.[19]

Besides, the *cis*-stereochemistry of the four-membered ring is set during the cyclization step to form the 2-azetidinone ring, and it is transferred unaltered during the further synthetic steps, except for compound **5**. NOE irradiation of proton H^c on compound **5** gave enhancements in the signals corresponding to H^d, methyl group (α to the carboxymethyl moiety), and 4-methoxyphenyl group (10%, 2%, and 7%, respectively), while NOE irradiation of H^b resulted in 16% enhancement in the signal corresponding to H^a. On the basis of these data a *syn*-H^a-H^b/*anti*-H^b-H^c/*syn*-H^c-H^d/*syn*-H^e-CH$_3$ relative stereochemistry was assigned for compound **5** (Figure 1).

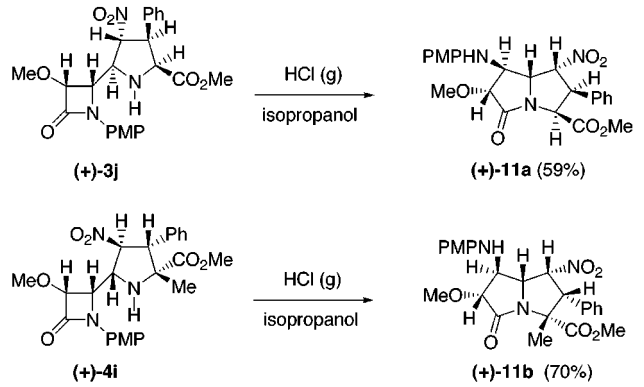
Scheme 5



Scheme 6



Scheme 7



For tricyclic compound (+)-**6c**, NOE irradiation of H^c resulted in enhancement of the signals corresponding to H^b and H^d (10% and 9%, respectively), while irradiation of H^c gave NOE enhancement of 2% on the methyl group (α to the carboxymethyl moiety) and NOE enhancement

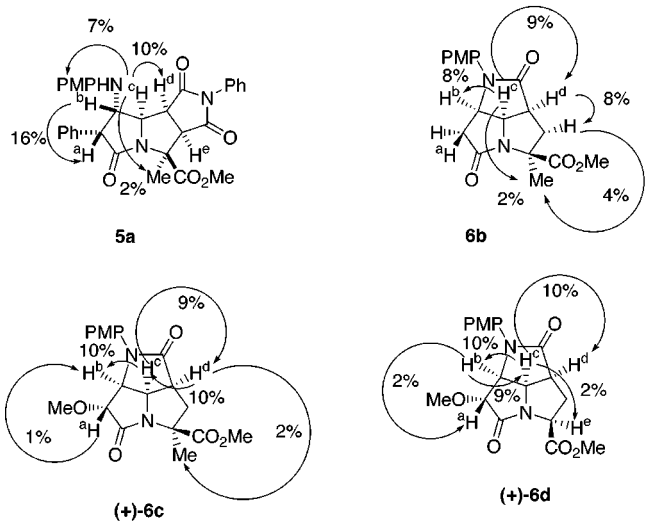


Figure 1. Selected NOE effects and stereochemistry of tricyclic compounds **5a**, **6b**, (+)-**6c**, and (+)-**6d**.

of 10% on H^c. Furthermore, NOE irradiation of H^a resulted in a small enhancement of the signal corresponding to H^b (1%). On the basis of these data, an *anti*-H^a-H^b/*syn*-H^b-H^c/*syn*-H^c-H^d/*syn*-H^d-CH_3 relative stereochemistry was assigned. NOE irradiation of proton H^b on compound (+)-**6d** resulted in 2% and 9% enhancements of the signals corresponding to H^a and H^c, respectively, while irradiation of H^c gave NOE enhancement of 10% on H^b, being assigned an *anti*-H^a-H^b/*syn*-H^b-H^c relative stereochemistry. Furthermore NOE irradiation of proton H^c resulted in enhancements of the signals corresponding to H^d and H^e (10% and 2%, respectively), which is in agreement with the proposed stereochemistry (Figure 1). Similar values were obtained when NOE experiments were carried out in pyrrolizidine derivatives **6a**,**b** and **6e**,**f**, being the stereochemistry immediately deduced by comparison with the above results. NOE irradiation of proton H^c on bicyclic compound (+)-**10** resulted in 9% and 2% enhancements of the signals corresponding to H^b and on the methyl group (α to the carboxymethyl moiety), respectively, while irradiation of H^b gave NOE enhancements of 1% and 9% in the signals corresponding to H^a and H^c, respectively (Figure 2). On the basis of these data, an *anti*-H^a-H^b/*syn*-H^b-H^c/*syn*-H^c-CH_3 relative stereochemistry was assigned.

Compounds **7a**−**d** have a five-membered ring fused to the γ-lactam. Absence of NOE enhancement was observed on H^a and H^c for compound (−)-**7a** upon irradiation of H^b, while NOE irradiation of H^c resulted in a 6% and 5% enhancement of the signals corresponding to H^d and the methyl group (α to the carboxymethyl moiety), respectively. Thus, a relative *anti*-stereochemistry was established for these moieties (H^a-H^b and H^b-H^c). Furthermore, irradiation of H^d give NOE enhancement of 7% on the signal corresponding to H^c and NOE enhancement of 5% on H^e, being assigned a *syn*-relative disposition between H^c and H^d. Irradiation of H^e on compound (−)-**7a** gave NOE enhancement of 2% in the signal corresponding to the methyl group (α to the carboxymethyl moiety), which is in agreement with the proposed stereochemistry (Figure 2). Absence of NOE enhancement was observed on H^a and H^c for compound (−)-**7b** upon irradiation of H^b being assigned an *anti*-H^a-H^b/*anti*-H^b-H^c relative stereochemistry. The irradiation of the signal

(19) It should be noted that the relative ^{1}H NMR chemical shift of the β-lactamic protons for the **3** and **4** pyrrolidinyl-β-lactams is a useful check of the relative stereochemistry. For any pair of **3** and **4** diastereoisomers, the β-lactamic hydrogens (H3 and H4) of the **3** isomers were ca. 0.2 ppm upfield of the analogous hydrogens of the **4** isomers. Besides, the chemical shift of H4 in the **3** isomer is always smaller than the chemical shift of H3, and by contrast the chemical shift of H3 in the **4** isomer is always smaller than the chemical shift of H4. The vicinal coupling constants of the two protons (H4 in the β-lactamic ring, hydrogen α to the nitrogen in the pyrrolidinic ring) located at the single bond connecting the two rings were diagnostic too for the **3** and **4** cycloadducts for the relative stereochemistry. The vicinal coupling constants for the major **3** isomers are ca. 9.0 Hz, suggesting a relative *anti*-stereochemistry for this connection, whereas these vicinal coupling constants for the minor **4** isomers are ca. 5.0 Hz, suggesting a relative *syn*-stereochemistry: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press: London, 1984; Vol. 3, Part B, p 115.

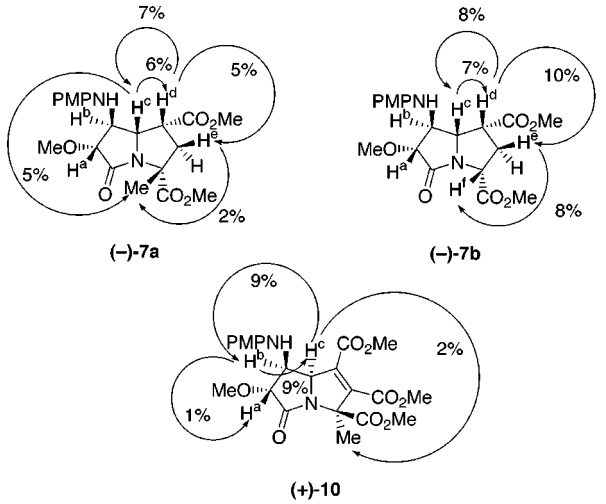


Figure 2. Selected NOE effects and stereochemistry of bicyclic compounds (−)-**7a**, (−)-**7b**, and (+)-**10**.

corresponding to H^c showed NOE enhancement (7%) of the neighboring H^d; while the irradiation of H^d resulted in a 8% and 10% enhancement of the signals corresponding to H^c and H^e, respectively. In addition, a 8% enhancement of the signal corresponding to H^f on irradiating H^e confirmed the proposed stereochemistry (Figure 2). Similar figures were observed when NOE experiments were carried out in pyrrolizidines **7c**,**d**, being the stereochemistry immediately deduced by comparison with the above results.

Compounds **11** have a bicyclic pyrrolizidine lactam structure. On compound (+)-**11a**, NOE irradiation of the signal corresponding to H^e induced a 17% enhancement of the H^f signal. NOE enhancements of H^c (13%) and the phenyl group (14%) on irradiation of H^d and NOE enhancements of H^d (13%) and the 4-methoxyphenyl group (20%) on irradiation of H^c were detected, whereas NOE enhancement could not be observed on the H^b signal when H^c was irradiated. These results evidence an *anti*-H^b-H^c/*syn*-H^c-H^d/*anti*-H^d-H^e/*syn*-H^e-H^f relative stereochemistry. For pyrrolizidinone (+)-**11b**, an *anti*-H^a-H^b/*anti*-H^b-H^c/*syn*-H^c-H^d relative stereochemistry was proposed on the basis of absence of enhancement on H^a and H^c upon NOE irradiation of H^b, together with a 16% NOE enhancement in the signal corresponding to H^d when H^c was irradiated. NOE irradiation of H^d give an enhancement of 7% on the signal corresponding to H^c and NOE enhancement of 7% on H^e, being assigned a *syn*-relative disposition between H^c and H^d. Besides, irradiation of H^e on compound (+)-**11b** gave 13% and 2% NOE enhancement of the signals corresponding to H^c and methyl group (α to the carboxymethyl moiety), respectively, which is in agreement with the proposed relative *syn*-stereochemistry (H^d-H^e, and H^e-CH_3) (Figure 3).

Conclusions. We have demonstrated that combination of 1,3-dipolar cycloaddition of 2-azetidinone-tethered azomethine ylides with rearrangement reactions on the 2-azetidinone ring is a powerful, hitherto unknown, strategy for the asymmetric synthesis of different highly functionalized enantiopure pyrrolizidine and diazatriquinane systems. The formation of pyrrolizidine lactams involves a selective C(O)−N bond cleavage in the four-membered ring, followed by a rearrangement under the reaction conditions. The relief of the strain associated with the four-membered ring on forming more stable

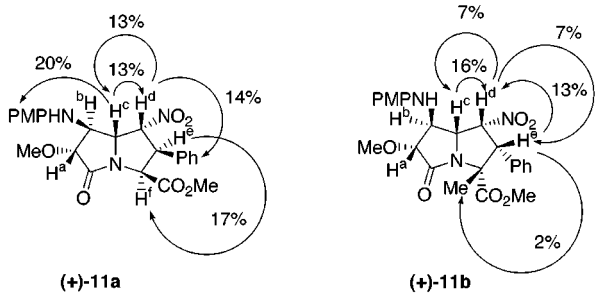


Figure 3. Selected NOE effects and stereochemistry of bicyclic compounds (+)-**11a** and (+)-**11b**.

polycyclic systems must be the driving force of the overall transformation. In addition, this methodology is very versatile, offering the possibility of obtaining a variety of conveniently functionalized pyrrolizidine derivatives just by changing the substituents in readily available 4-oxoazetidine-2-carbaldehydes, α-amino esters, or dipolarophiles.

Experimental Section

General. General experimental data and procedures have been previously reported.[14a] NMR spectra were recorded in $CDCl_3$ solutions, except when otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm), or $CDCl_3$ (^{13}C, 77.0 ppm). All commercially available compounds were used without further purification.

General Procedure for the Synthesis of Cycloadducts 3 and 4. A solution of the appropriate 4-azetidinone-2-carbaldehyde **1** (1.00 mmol) in dichloromethane (7 mL) was added dropwise to a stirred solution of 4 Å molecular sieves (2.0 g) and the corresponding α-amino ester (1.50 mmol) in dichloromethane (3 mL) at room temperature. After stirring for 2 h at room temperature, the mixture was filtered through a plug of Celite. The solvent was removed under reduced pressure, giving imines **2** in quantitative yield. The crude product was used for the next step without any further purification.

To a solution of the appropriate imine **2** (1.00 mmol) in toluene (6 mL) were sequentially added silver acetate (1.20 mmol), the dipolarophile (phenylmaleimide, methyl acrylate, or dimethyl fumarate) (1.50 mmol), and triethylamine (1.20 mmol), and the reaction mixture was stirred at room temperature for 40 h. Saturated aqueous NH_4Cl (1 mL) was added, and the mixture was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes or acetate/dichloromethane mixtures gave analytically pure compounds **3** and **4**. Spectroscopic and analytical data for some representative pure forms of **3** and **4** follow.[20]

Cycloadduct 3d. From 240 mg (1.17 mmol) of the aldehyde **1d** and 181 mg (1.77 mmol) of l-alanine methyl ester, after column chromatography eluting with ethyl acetate/hexanes (3:1), 210 mg (48%) of the compound **3d** was obtained. Colorless oil. ^1H NMR ($CDCl_3$): δ 1.28 (s, 3H), 1.86 (dd, 1H, J = 13.5, 7.6 Hz), 2.62 (dd, 1H, J = 13.5, 5.1 Hz), 2.65 (dd, 1H, J = 15.2, 2.5 Hz), 3.03 (dd, 1H, J = 15.2, 5.1 Hz), 3.05 (m, 1H), 3.59 (dd, 1H, J = 9.0, 7.3 Hz), 3.62 (s, 3H), 3.70 and 3.71 (s, each 3H), 4.07 (m, 1H), 6.79 and 7.50 (d, each 2H, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$): δ 176.3, 173.1, 164.5, 156.6, 131.3, 120.6, 114.2, 65.9, 65.5, 55.6, 54.3, 52.6, 52.1, 46.4, 40.7, 40.0, 27.3. IR ($CHCl_3$, cm^{-1}): ν 3340, 1745. MS (CI), m/z: 364 (M^+ + 1, 100), 301 (M^+, 40). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.45; H, 6.54; N, 7.77.

(20) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

Preparation of Cycloadducts (+)-3f and (+)-4f. From 708 mg (3.00 mmol) of the aldehyde (+)-**1e** and 485 mg (5.50 mmol) of glycine methyl ester, after column chromatography eluting with ethyl acetate/dichloromethane (2:8), 540 mg (46%) of the less polar compound (+)-**3f** and 235 mg (20%) of the more polar compound (+)-**4f** were obtained.

Cycloadduct (+)-3f. Colorless oil. $[\alpha]_D = +170.9$ (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.33 (m, 2H), 3.29 (dd, 1H, J = 12.5, 6.6 Hz), 3.53 (dd, 1H, J = 9.3, 6.6 Hz), 3.64 (s, 3H), 3.73 (m, 4H), 3.75 and 3.78 (s, each 3H), 4.42 (dd, 1H, J = 9.3, 5.4 Hz), 4.57 (d, 1H, J = 5.4 Hz), 6.85 and 7.54 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 173.9, 173.6, 165.6, 156.8, 130.7, 120.3, 114.2, 83.2, 63.5, 60.5, 59.8, 59.3, 55.5, 52.3, 51.9, 44.9, 33.4. IR ($CHCl_3$, cm^{-1}): ν 3333, 1744. MS (CI), *m*/*z*: 392 ($M^+ + 1$, 100), 391 (M^+, 50). Anal. Calcd for $C_{19}H_{23}N_2O_7$: C, 58.31; H, 5.92; N, 7.16. Found: C, 58.43; H, 5.84; N, 7.08.

Cycloadduct (+)-4f. Colorless solid. Mp 157−158 °C (hexanes/ethyl acetate). $[\alpha]_D = +95.0$ (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.34 (m, 2H), 2.88 (m, 1H), 3.59 (s, 3H), 3.66 (m, 4H), 3.73 (m, 4H), 3.77 (s, 3H), 4.64 (d, 1H, J = 5.1 Hz), 4.80 (dd, 1H, J = 5.9, 5.1 Hz), 6.85 and 7.30 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 173.4, 173.0, 165.1, 157.1, 129.4, 121.0, 114.3, 83.7, 61.9, 59.4, 58.1, 57.4, 55.4, 52.1, 51.7, 44.7, 33.5. IR ($CHCl_3$, cm^{-1}): ν 3335, 1743. MS (EI), *m*/*z*: 392 ($M^+ + 1$, 42), 391 (M^+, 100). Anal. Calcd for $C_{20}H_{26}N_2O_7$: C, 59.10; H, 6.45; N, 6.89. Found: C, 59.18; H, 6.59; N, 6.99.

Preparation of Cycloadducts (+)-3h and (+)-4h. From 200 mg (0.851 mmol) of the aldehyde (+)-**1e** and 114 mg (1.28 mmol) of glycine methyl ester, after column chromatography eluting with ethyl acetate/hexanes (1:1), 171 mg (53%) of the less polar compound (+)-**3h** and 45 mg (14%) of the more polar compound (+)-**4h** were obtained.

Cycloadduct (+)-3h. Pale yellow oil. $[\alpha]_D = +38.0$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.57 (m, 2H), 3.64 (s, 3H), 3.74 (m, 4H), 3.76 and 3.77 (s, each 3H), 4.03 (dd, 1H, J = 6.9, 6.6 Hz), 4.37 (dd, 1H, J = 9.0, 5.1 Hz), 4.51 (d, 1H, J = 5.1 Hz), 6.90 and 7.50 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 172.4, 172.3, 172.1, 165.5, 156.9, 130.6, 120.4, 114.3, 83.2, 63.0, 62.4, 60.3, 59.8, 55.6, 52.8, 52.6, 52.4, 50.7, 49.3. IR ($CHCl_3$, cm^{-1}): ν 3338, 1740. MS (EI), *m*/*z*: 451 ($M^+ + 1$, 42), 450 (M^+, 100). Anal. Calcd for $C_{21}H_{26}N_2O_9$: C, 55.99; H, 5.82; N, 6.22. Found: C, 56.07; H, 5.74; N, 6.28.

Cycloadduct (+)-4h. Pale yellow solid. Mp 103−104 °C (hexanes/ethyl acetate). $[\alpha]_D = +90.9$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.37 (dd, 1H, J = 7.3, 4.1 Hz), 3.57 (m, 1H), 3.63 and 3.66 (s, each 3H), 3.73 and 3.76 (s, each 3H), 3.78 (s, each 3H), 3.91 (m, 2H), 4.61 (d, 1H, J = 5.1 Hz), 4.75 (dd, 1H, J = 5.1, 4.9 Hz), 6.86 and 7.32 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 172.7, 171.7, 171.4, 165.0, 157.0, 129.5, 120.4, 114.5, 83.7, 62.7, 60.5, 59.3, 56.8, 55.5, 52.6, 52.5, 52.2, 51.4, 49.5. IR ($CHCl_3$, cm^{-1}): ν 3341, 1742. MS (CI), *m*/*z*: 451 ($M^+ + 1$, 100), 450 (M^+, 29). Anal. Calcd for $C_{21}H_{26}N_2O_9$: C, 55.99; H, 5.82; N, 6.22. Found: C, 55.91; H, 5.76; N, 6.12.

Preparation of Cycloadducts (+)-3k and (+)-4k. From 200 mg (0.851 mmol) of the aldehyde (+)-**1e**, 131 mg (1.28 mmol) of L-alanine methyl ester, and 182 mg (1.28 mmol) of dimethyl acetylenedicarboxylate, by heating at 40 °C for 24 h and after column chromatography eluting with dichloromethane/ethyl acetate (10:1), 208 mg (47%) of the less polar compound (+)-**3k** and 26 mg (6%) of the more polar compound (+)-**4k** were obtained.

Cycloadduct (+)-3k. Pale yellow oil. $[\alpha]_D = +145.4$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.57 (s, 3H), 3.51 and 3.61 (s, each 3H), 3.70 and 3.76 (s, each 3H), 3.85 (s, 3H), 4.51 (d, 1H, J = 4.9 Hz), 4.70 (m, 2H), 6.77 and 7.35 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 172.4, 165.3, 164.5, 163.1, 156.3, 146.1, 139.3, 130.9, 119.8, 113.6, 82.3, 72.3, 64.5, 59.6, 59.4, 55.4, 52.5, 52.3, 52.1, 25.7. IR ($CHCl_3$, cm^{-1}): ν 3338, 1758, 1745. MS (EI), *m*/*z*: 463 ($M^+ + 1$, 32), 462 (M^+, 100). Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14; H, 5.67; N, 6.06. Found: C, 57.22; H, 5.61; N, 5.98.

Cycloadduct (+)-4k. Pale yellow oil. $[\alpha]_D = +56.2$ (*c* 0.7, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.57 (s, 3H), 3.40 and 3.54 (s, each 3H), 3.77 and 3.78 (s, each 3H), 3.81 (s, 3H), 4.61 (m, 2H), 4.90 (d, 1H, J = 5.4 Hz), 6.85 and 7.30 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 173.2, 165.3, 163.0, 156.6, 149.1, 145.0, 135.8, 130.7, 118.9, 114.5, 83.5, 73.5, 63.2, 59.9, 59.7, 55.6, 52.8, 52.5, 52.2, 25.5. IR ($CHCl_3$, cm^{-1}): ν 3342, 1756, 1744. MS (CI), *m*/*z*: 463 ($M^+ + 1$, 100), 462 (M^+, 20). Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14; H, 5.67; N, 6.06. Found: C, 56.98; H, 5.73; N, 6.10.

HCl(g)-Promoted Reaction of Pyrrolidinyl-*β*-lactams 3 and 4. General Procedure for the Synthesis of Diazatriquinanes 6 and Pyrrolizidines 7. HCl(g) was bubbled, during 1 h, through an unstirred solution of the appropriate cycloadduct **3** or **4** (0.4 mmol) in 2-propanol (6 mL) and then left in a sealed vessel for 36 h. The reaction mixture was concentrated under reduced pressure, diluted with dichloromethane (10 mL), washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and concentrated under reduced pressure. After purification by flash chromatography, eluting with hexanes/ethyl acetate, the appropriate pyrrolizidinones **5** and **6** were obtained in analytically pure form.

Tricycle 6b. From 144 mg (0.384 mmol) of adduct **3d**, 90 mg (68%) of compound **6b** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 1/15). Mp 217−218 °C (hexanes/ethyl acetate). ^1H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.74 (dd, 1H, J = 14.0, 8.3 Hz), 2.05 (m, 2H), 2.45 (dd, 1H, J = 8.3, 5.8 Hz), 2.76 (d, 1H, J = 14.0 Hz), 3.32 and 3.42 (s, each 3H), 3.74 (t, 1H, J = 5.2 Hz), 3.84 (m, 1H), 6.60 and 7.05 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 172.4, 172.3, 171.6, 170.3, 158.1, 129.3, 125.1, 114.7, 82.2, 63.1, 62.6, 62.1, 58.5, 55.5, 52.7, 45.3, 44.4, 24.2. IR ($CHCl_3$, cm^{-1}): ν 1751, 1701. MS (CI), *m*/*z*: 344 ($M^+ + 1$, 100), 374 (M^+, 16). Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 60.88; H, 5.73; N, 8.05.

Tricycle (+)-6c. From 162.4 mg (0.4 mmol) of adduct (+)-**3e**, 89.8 mg (60%) of compound (+)-**6c** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 1/1). $[\alpha]_D = +20.5$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.46 (s, 3H), 2.26 (dd, 1H, J = 14.2, 7.8 Hz), 2.98 (d, 1H, J = 14.2 Hz), 3.07 (dd, 1H, J = 7.8, 5.6 Hz), 3.40 (s, 3H), 3.55 (s, 1H), 3.66 and 3.74 (s, each 3H), 4.46 (d, 1H, J = 4.6 Hz), 4.72 (dd, 1H, J = 5.6, 4.6 Hz), 6.85 and 7.21 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 172.6, 171.4, 170.3, 158.1, 129.3, 125.1, 114.7, 82.2, 63.1, 62.6, 62.1, 58.5, 55.5, 52.7, 45.3, 44.4, 24.2. IR ($CHCl_3$, cm^{-1}): ν 1744, 1701. MS (EI), *m*/*z*: 375 ($M^+ + 1$, 18), 374 (M^+, 100). Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.83; H, 5.82; N, 7.56.

Tricycle (+)-6d. From 108 mg (0.28 mmol) of adduct (+)-**3f**, 60 mg (61%) of compound (+)-**6d** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 1/3). $[\alpha]_D = +6.0$ (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.70 (m, 2H), 3.05 (dd, 1H, J = 6.1, 5.6 Hz), 3.39 (s, 3H), 3.56 (s, 1H), 3.70 and 3.74 (s, each 3H), 4.43 (dd, 1H, J = 8.5, 3.4 Hz), 4.47 (d, 1H, J = 4.4 Hz), 4.66 (dd, 1H, J = 5.6, 4.4 Hz), 6.85 and 7.30 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 172.4, 171.3, 169.9, 158.3, 129.2, 125.6, 114.8, 82.1, 63.1, 62.9, 58.5, 56.6, 55.6, 52.7, 44.5, 35.5. IR ($CHCl_3$, cm^{-1}): ν 1751, 1701. MS (CI), *m*/*z*: 361 ($M^+ + 1$, 100), 360 (M^+, 22). Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.13; H, 5.89; N, 7.71.

Tricycle (+)-6e. From 100 mg (0.212 mmol) of adduct (+)-**3g**, 76 mg (70%) of compound (+)-**6e** was obtained as a colorless solid after purification by flash chromatography (hexanes/ethyl acetate 1/2). Colorless solid. Mp 132−133 °C (hexanes/ethyl acetate). $[\alpha]_D = +54.2$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.49 (s, 3H), 3.43 (s, 3H), 3.46 (d, 1H, J = 5.4 Hz), 3.59 (s, 1H), 3.75 and 3.77 (s, each 3H), 3.79 (s, 3H), 3.99 (s, 1H), 4.53 (d, 1H, J = 4.8 Hz), 4.97 (dd, 1H, J = 5.7, 4.8 Hz), 6.93 and 7.23 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 171.3, 170.8, 170.1, 169.6, 158.2, 128.9, 125.1, 114.7, 82.0, 65.4, 62.4, 62.2, 58.4, 58.3, 55.4, 53.1, 52.4, 48.4, 19.5. IR ($CHCl_3$, cm^{-1}): ν 1746, 1703. MS (EI), *m*/*z*: 433 ($M^+ + 1$, 32), 432 (M^+, 100). Anal. Calcd for $C_{21}H_{24}N_2O_8$: C, 58.33; H, 5.59; N, 6.48. Found: C, 58.39; H, 5.51; N, 6.40.

Tricycle (+)-6f. From 80 mg (0.21 mmol) of adduct (+)-**3h**, 45 mg (57%) of compound (+)-**6f** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 1/1). $[\alpha]_D = +10.8$ (*c* 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.29 and 1.31 (d, each 3H, J = 6.6 Hz), 3.45 (s, 3H), 3.47 (d,

1H, J = 6.0 Hz), 3.62 (s, 1H), 3.82 (m, 4H), 3.84 (s, 3H), 4.37 (d, 1H, J = 3.0 Hz), 4.55 (d, 1H, J = 4.2 Hz), 4.83 (dd, 1H, J = 6.0, 4.2 Hz), 5.09 (m, 1H, J = 6.6 Hz), 6.95 and 7.32 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 170.8, 170.7, 170.3, 168.5, 158.4, 128.8, 125.6, 114.7, 81.8, 77.2, 70.1, 62.9, 62.6, 60.1, 58.3, 55.5, 53.7, 52.9, 47.7, 21.6. IR ($CHCl_3$, cm^{-1}): ν 1751, 1707. MS (EI), m/z: 447 (M^+ + 1, 32), 446 (M^+, 100). Anal. Calcd for $C_{22}H_{26}N_2O_8$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.11; H, 5.93; N, 6.37.

Bicycle (−)-7a. From 102 mg (0.250 mmol) of adduct (+)-**4e**, 56 mg (55%) of compound (−)-**7a** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 2/1). $[\alpha]_D = -33.93$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.58 (s, 3H), 2.10 (dd, 1H, J = 13.8, 7.8 Hz), 2.93 (d, 1H, J = 13.8 Hz), 3.05 (t, 1H, J = 7.8 Hz), 3.39 and 3.52 (s, each 3H), 3.66 and 3.68 (s, each 3H), 3.88 (dd, 1H, J = 8.4, 7.8 Hz), 3.94 (d, 1H, J = 8.7 Hz), 4.35 (dd, 1H, J = 8.7, 8.4 Hz), 6.71 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 171.6, 170.6, 170.5, 168.2, 158.3, 129.2, 117.2, 114.7, 77.2, 64.0, 62.6, 61.3, 58.8, 55.6, 52.7, 43.1, 42.4, 22.8. IR ($CHCl_3$, cm^{-1}): ν 3340, 1740, 1711. MS (EI), m/z: 407 (M^+ + 1, 20), 406 (M^+, 100). Anal. Calcd for $C_{20}H_{26}N_2O_7$: C, 59.10; H, 6.45; N, 6.89. Found: C, 59.00; H, 6.53; N, 6.81.

Bicycle (−)-7b. From 110 mg (0.281 mmol) of adduct (+)-**4f** in methanol (5 mL), 82 mg (74%) of compound (−)-**7b** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 1/1). $[\alpha]_D = -28.0$ (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.48 (ddd, 1H, J = 13.9, 9.0, 7.6 Hz), 2.73 (ddd, 1H, J = 13.9, 2.7, 2.2 Hz), 3.07 (ddd, 1H, J = 7.6, 7.3, 2.2 Hz), 3.39 and 3.52 (s, each 3H), 3.69 and 3.70 (s, each 3H), 3.83 (dd, 1H, J = 8.0, 7.3 Hz), 4.03 (d, 1H, J = 8.5 Hz), 4.12 (dd, 1H, J = 9.0, 2.7 Hz), 6.80 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 170.6, 169.4, 169.0, 153.2, 141.0, 116.3, 114.7, 88.5, 64.1, 61.2, 58.8, 55.6, 54.8, 52.6, 52.2, 41.9, 34.5. IR ($CHCl_3$, cm^{-1}): ν 3344, 1744, 1705. MS (CI), m/z: 393 (M^+ + 1, 100), 392 (M^+, 34). Anal. Calcd for $C_{19}H_{24}N_2O_7$: C, 58.16; H, 6.16; N, 7.14. Found: C, 58.28; H, 6.26; N, 7.08.

Bicycle (−)-7c. From 80 mg (0.172 mmol) of adduct (+)-**4g**, 59 mg (73%) of compound (−)-**7c** was obtained as a pale yellow oil after purification by flash chromatography (hexanes/ethyl acetate 1/1). $[\alpha]_D = -67.7$ (c 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 3H), 3.33 and 3.55 (s, each 3H), 3.70 and 3.75 (s, each 3H), 3.87 (s, 3H), 3.90 (d, 1H, J = 8.4 Hz), 3.97 (dd, 1H, J = 9.1, 8.4 Hz), 4.06 (dd, 1H, J = 9.4, 9.1 Hz), 4.20 (d, 1H, J = 9.1 Hz), 6.75 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 169.9, 169.4, 168.7, 168.3, 153.0, 138.2, 115.8, 114.6, 77.5, 63.9, 61.5, 60.9, 55.5, 55.5, 53.1, 52.7, 52.4, 44.6, 42.8, 18.1. IR ($CHCl_3$, cm^{-1}): ν 3342, 1747, 1718. MS (EI), m/z: 463 (M^+ + 1, 31), 462 (M^+, 100). Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14; H, 5.67; N, 6.06. Found: C, 57.06; H, 5.61; N, 6.16.

HCl(aq)-Promoted Reaction of Pyrrolidinyl-β-lactam (+)-3j. Synthesis of Bicycle (+)-10. To a solution of the cycloadduct (+)-**3k** (126 mg, 0.272 mmol) in methanol (18 mL) was added a catalytic amount (a few drops) of 37% aqueous hydrochloric acid. The resulting solution was heated under reflux for 18 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The mixture was diluted with dichloromethane (15 mL), washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate (1:1) gave 65 mg (52%) of the pyrrolizidinone (+)-**10** as a colorless oil. $[\alpha]_D = +18.5$ (c 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.69 (s, 3H), 3.51 and 3.68 (s, each 3H), 3.75 and 3.83 (s, each 3H), 3.89 (s, 3H), 4.27 (dd, 1H, J = 12.4, 4.2 Hz), 4.44 (d, 1H, J = 12.0 Hz), 5.56 (d, 1H, J = 4.5 Hz), 6.60 and 6.77 (m, each 2H). ^{13}C NMR ($CDCl_3$): δ 172.2, 169.1, 162.1, 161.5, 153.2, 143.5, 139.8, 134.6, 115.9, 115.1, 85.8, 71.3, 70.6, 60.1, 58.5, 55.9, 53.7, 53.0, 52.7, 20.6. IR ($CHCl_3$, cm^{-1}): ν 3240, 1736, 1720, 1711. MS (CI), m/z: 463 (M^+ + 1, 100), 462 (M^+, 20). Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14; H, 5.67; N, 6.06. Found: C, 57.08; H, 5.61; N, 6.00.

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Supporting Information Available: Spectroscopic and analytical data for isomerically pure compounds **3a**−**c**, (+)-**3e**, (+)-**3g**, (+)-**3i**, (+)-**3j**, **4a**, **4b**, (+)-**4e**, (+)-**4g**, (+)-**4i**, (+)-**4j**, **5**, **6a**, (+)-**8**, (−)-**9**, (+)-**11a**, and (+)-**11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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